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TITLE: Fibroblast Growth Factor Regeneration of Tympanic Membrane Perforations

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14. ABSTRACT

Tympanic membrane perforation (TMP) is the most common primary blast injury in the current conflicts in Afghanistan and Iraq occurring in 10-35% of service members wounded by combat explosions. The hypothesis to be tested in this Phase I open label dose-finding study is that topical application of fibroblast growth factor-1 to the TMP will result in closure of chronic TM perforations. Primary aims are: 1) to evaluate the safety and tolerability of FGF-1 to treat chronic non-healing tympanic membrane perforations; 2) to determine the maximum tolerated- or optimal biologic-dose of FGF-1 required to achieve complete closure of chronic non-healing tympanic membrane perforations; 3) to determine efficacy of TMP closure at the optimal biologic dose in a placebo controlled blinded phase II study. To date, an investigational new drug (IND) number has been assigned by the FDA for use of FGF-1 in this indication. Institutional review board approval is currently being sought at the local level. Once approved at the local level, the protocol will be submitted to the USAMRMC's Office of Research Protections for review and approval. If successful, this study will change the paradigm for treatment of tympanic membrane perforations in military and civilian populations alike. Both will have complete recovery of TM function with middle ear protection without surgical intervention and reduction of recovery time. The transition of this application may lead to adding of inner ear protectants to help recover associated sensorineural hearing loss attendant with blast injuries.

15. SUBJECT TERMS
Fibroblast growth factor, regeneration and repair of tympanic membrane perforations

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INTRODUCTION:

The objective of the study is to determine if topical application of fibroblast growth factor-1 (FGF-1) to tympanic membrane perforations will result in closure of chronic perforations. The primary aims are: 1) to evaluate the safety and tolerability of FGF-1 to treat chronic non-healing tympanic membrane perforations; 2) to determine the maximum tolerated- or optimal biologic-dose of FGF-1 required to achieve complete closure of chronic non-healing tympanic membrane perforations; 3) to determine efficacy of tympanic membrane perforation closure at the optimal biologic dose in a placebo controlled blinded phase II study. Secondary aims are: 1) to determine the time to closure of tympanic membrane perforation as documented by otoscopy and by blinded photographic and tympanogram documentation; and 2) to measure blinded changes in pure-tone and speech discrimination scores pre and post-treatment. If successful, this study will change the paradigm for treatment of tympanic membrane perforations in military and civilian populations alike. Patients will have complete recovery of tympanic membrane function without surgical intervention and reduction of recovery time.

BODY:

Recently, the Food and Drug Administration (FDA) removed the full clinical hold on the Investigational New Drug (IND) application (IND 114233) to use FGF-1 in a topical application for the repair of chronic tympanic membrane perforations (Sub-task 1.1). Animal toxicology studies have been completed, and the FDA concluded that all clinical hold issues had adequately been addressed and that the clinical trial of FGF-1 can be initiated. The findings in the animal study indicated high dose FGF-1 (7 μg) was well tolerated as assessed by clinical observations, body weight, auditory brainstem response, functional observation battery testing, hematology, clinical chemistry and ear histopathology. There did not appear to be any evidence of local toxicity or local irritation in the ear as a direct result of FGF-1 treatment indicating that FGF-1 treatment did not result in local or systemic toxicity or injury to the ear structures or to the hair cells under the conditions used in the study.

With the removal of the full clinical hold, we have now submitted an application, the protocol, and consent form to the Institutional Review Board (IRB) at The Ohio State University for review and approval (Sub-task 1.3). Once approval is received from the local IRB, the protocol and consent form will be submitted to the USAMRMC's Office of Research Protections for review and approval

Additionally, we will begin to work with our data management center to create the electronic case report forms (eCRFs) to be used in the study and initiate training on the data collection system REDCap (Sub-task 1.7).

KEY RESEARCH ACCOMPLISHMENTS:

- Approval of Investigational New Drug Application (IND), IND 114233
- Submission of research protocol and supporting materials to local Institutional Review Board for review and approval

REPORTABLE OUTCOMES:

1. FDA Correspondence, removing full clinical hold, IND 114233

CONCLUSION:

The IND approval process took much longer than anticipated. With completion of that task, we can progress towards initiation of the Phase I clinical trial, once the appropriate human subjects research approvals have been obtained.

REFERENCES:

Not applicable

APPENDICES:

1. FDA Correspondence, IND 114233

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114233

REMOVE FULL CLINICAL HOLD

Phage Pharmaceuticals, Inc.
Attention: Judi Appleman
Assistant Director for Regulatory Affairs
6868 Nancy Ridge Drive, #100
San Diego, California 92121

Dear Ms. Appleman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for FGF-1.

We also refer to your amendment dated August 19, 2013, which provides a complete response to our February 17, 2012, letter which cited the reasons for placing this IND on clinical hold and the information needed to resolve the clinical hold issues.

We have completed the review of your submission, and have concluded that you have adequately addressed the clinical hold issue and the clinical trial may be initiated.

ADDITIONAL IND RESPONSIBILITIES

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

  If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

  If your IND is not in eCTD format:

  - you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);

- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the date clinical studies were permitted to begin) [21 CFR 312.33].

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT
09/18/2013

SUPPORTING DATA:

Not applicable